activator (u-PA), amino acids 1-138, hereafter referred to as ATF, can be constructed by deleting the DNA sequences encoding amino acids 139 till 401 in an expression plasmid for the full length u-PA using a polymerase chain reaction (PCR) with the following oligonucleotides: 5' - cccgggctttttccatctgcgcagtc -3' (SEQ ID NO.: 1) and 5' - agggtcaccaaggaagagaatggc -3' (SEQ ID NO.: 2). After amplification by PCR the newly formed DNA fragment can be circularized by ligation to restore the circular character of the expression plasmid. In this way an expression plasmid encoding the ATF and the C terminal last 11 amino acid residues including the stop codon can be constructed.

Amend the paragraph at page 8, line 34, through page 9, line 18, to read as follows:

DNA fragments encoding amino acid residues 36-93 of bovine pancreatic trypsin inhibitor (BPTI) and the homologous amino acid residues of bovine spleen trypsin inhibitor (BSTI) can be isolated by performing a PCR reaction on gnomic DNA isolated for bovine aortic endothelial cells using the following oligonucleotides: 5' - *tc*gcg*a*cctgacttctgcctagagc - 3' (SEQ ID NO.: 3) covering nucleotides 2509 to 2533 (with modifications, indicated in *italics,* in the 5' region of the oligonucleotide to introduce a NruI site (underlined) for cloning purposes) of the BPTI gene according to the published sequence (GENBANK, BTBPTIG), and nucleotide 2442 to 2462 of the BSTI gene according to the published sequence (GENBANK, BTBSTIG) and 5' ggt*cac*ccagggcccaata*tt*accacc -3' (SEQ ID NO.: 4) covering nucleotides 2677 to 2704 of the

BPTI gene and 2610 to 2636 of the BSTI gene (modified in the indicated nucleotide *(italics)* to introduce a BstEII and a SspI site respectively (underlined). The amplified DNA fragments then were cloned into an appropriate plasmid vector, pCRII or pUC13, and then the exact sequence of the amplified DNA fragments in the isolated clones was analyzed to differentiate between BPTI and BSTI which have a very high degree of homology.

Amend the paragraph at page 9, lines 21-32, to read as follows:

The DNA fragment encoding amino acids 1 to 207 of the human tissue inhibitor of metalloproteinase typ 1 is isolated by performing a reverse transcriptase polymerase chain reaction on total RNA isolated from human foreskin fibroblasts by using the following oligonucleotides 5' - agagagacaccagagaacccaccat - 3' (SEQ ID NO.: 5) covering nucleotide 41 to 65 of the human TIMP-1 cDNA (according to the sequence in GENBANK HSTIMPR) and 5' - tcattgt ccgaagaaagatgggag -3' (SEQ ID NO.: 6) covering nucleotides740 till 755. The amplified DNA fragment was cloned into an appropriate host vector, pUC13, and then the exact sequence of the amplified DNA fragment in the isolated clones was analyzed.

A 3

Amend the paragraph at page 10, lines 18-30, to read as follows:

Starting from a pCRII plasmid in which a 1373 base pair fragment of the uPA cDNA was

A 4

cloned, a PCR reaction with the oligonucleotides 5'- *ccc*gggctttttccatctgcgcagtc - 3' (SEQ ID NO.: 1) (SmaI site underlined and nucleotides changed in *italics)* and 5' - a*gggtc*accaaggaagagaatggc -3' (SEQ ID NO.: 2) (BstEII site underlined and nucleotide changed in *italics)* was performed as described in example 1 to make a pCRII-ATF plasmid (see figure 1). Subsequently this pCRII-ATF plasmid was digested with the restriction enzymes SmaI and BsteII. In parallel the pCRII-BPTI plasmid was digested with the restriction enzymes NruI and BsteII and the BPTI containing fragment was cloned into the pCRII-ATF plasmid (see figure 2). The construction pCRII-ATF-BPTI is shown in Fig. 2.

Amend the paragraph at page 11, lines 23-29, to read as follows:

A5

Starting from a pCRII plasmid in which a 1373 base pair fragment of the uPA cDNA was cloned, a PCR reaction with the oligonucleotides 5'-cccgggctttttccatctgcgcagtc -3' (SEQ ID NO.: 1) and 5'-agggtcaccaaggaagagaatggc - 3' (SEQ ID NO.: 2) was performed as described in example 1 to make a pCRII-ATF plasmid (see figure 1). Subsequently this pCRII-ATF plasmid was digested with the restriction enzymes SmaI and BsteII.

Amend the paragraph at page 11, line 30, through page 12, line 3, to read as follows:

A6

In parallel a fragment of the cDNA of TIMP1 in pUC13-TIMP1 encoding amino acid

residues 1 to 184 of the mature protein, but lacking the signal peptide and the stop codon, was amplified using the following oligonucleotides 5'-tcgcgatgcacctgtgtcccacc -3' (SEQ ID NO.: 7) and 5'-ggtcacccaaatattggctatgtgggaccgcaggg -3' (SEQ ID NO.: 8). These oligonucleotides contain recognition sites for the restriction enzymes NruI (first oligonucleotide, underlined) and BstEII and Ssp1 respectively (second oligonucleotide, underlined); these sites are needed for the cloning procedure.

Amend the paragraph at page 12, line 26, through page 13, line 2, to read as follows:

Starting from a pCRII plasmid in which a 1373 base pair fragment of the uPA cDNA was cloned, a PCR reaction with the oligonucleotides 5'- cccgggctttttttccatctgcgcagtc-3' (SEQ ID NO.: 1) and 5'-agggtcaccaaggaagagaatggc - 3' (SEQ ID NO.: 2) was performed as described in example 1 to make a pCRII-ATF plasmid (see figure 1). Subsequently on this pCRII-ATF plasmid a PCR reaction was performed using the oligonucleotides 5'-aatattattgaacttcatcaagttcc-3' (SEQ ID NO.: 9) and 5'-gactctagagcaaaaatgacaaccag-3' (SEQ ID NO.: 10) and the resulting DNA fragment was cloned into the pCRII cloning vector. In this way the signal peptide of u-PA is removed and a SspI restriction enzyme recognition site is introduced (underlined). The resulting plasmid DNA is designated pCRIIATF'.

Amend the paragraph at page 13, lines 3-11, to read as follows:

In parallel a fragment of the cDNA of TIMP1 in pUC13-TIMP1 encoding amino acid residues -23 to 184 of the TIMP-1 protein, including the signal peptide but lacking the stop codon, was amplified using the oligonucleotides 5'-agagagacaccagagaacccaccat-3' (SEQ ID NO.: 11) and 5'-aatattggctatctgggaccgcagg-3' (SEQ ID NO.: 12) containing a recognition site for the restriction enzyme Ssp1 (underlined) and cloned into a pCRII cloning vector. The resulting plasmid DNA is designated pCRII-TIMP1*.

Amend page 18, line 20, to read as follows:

Nucleotide sequence (SEQ ID NO.: 13):

CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.